Use of Fixed 50% Nitrous Oxide–Oxygen Mixture for Lumbar Punctures in Pediatric Patients

To the Editors:

A lumbar puncture is one of the most commonly painful procedures performed in pediatric medical practice. Despite evidence to suggest that analgesia and sedation are both efficacious and safe in children, clinical practices do not adhere to these findings. A study carried out in 1993 by Quinn et al. showed that 95% of children who had a lumbar puncture performed in a pediatric emergency department did not receive any local anesthesia. Another recent report found that only less than 25% of children had received any form of pain management during the execution of a lumbar puncture. These results demonstrate the ongoing issue of the lack of pain treatment in children. Although numerous studies have shown that children have similar physiological pain responses as adults, children often receive less pain medication compared with adults, under similarly painful conditions. Therefore, the provision of adequate sedation and analgesia for children undergoing painful procedures in the emergency department is a challenging proposition.

The ideal agent for sedation during a brief but painful procedure must be safe and easy to administer, provide adequate amnesia, and have a rapid onset and recovery time. A good choice for this kind of procedures in children is the equimolecular mixture of oxygen and nitrous oxide (EMONO). Nitrous oxide, a gas with analgesic properties, has been known about for more than 2 centuries. Its modern use outside the operating theater started in 1961 when Tunstall introduced a stable mixture of nitrous oxide and oxygen in equal proportions in a single cylinder for the relief of pain during labor. From that moment on, the anxiolytic and the analgesic properties of the EMONO have been very useful to relieve numerous painful procedures both in adults and children. When used in low concentrations, nitrous oxide allows the maintenance of the laryngeal reflex and has a well-documented safety record. The technique requires minimal advance preparation of staff, equipment, and the patient. The mask-administered gas has rapid onset and is short acting; an empty stomach is not required, and it provides excellent control of pain, anxiety, awareness, and motion during the uncomfortable procedure. Postoperatively, memory of the event is blunted, and no monitoring is necessary.

The purpose of this study was to analyze the safety and effectiveness of EMONO when it is used as method of sedation and analgesia during lumbar punctures in pediatric patients.

METHODS

We prospectively evaluated all lumbar punctures performed during a 16-month period (February 2007 through June 2009) in the emergency department of a large urban children’s tertiary care hospital. All physicians who were working in the emergency department during that period were asked to participate in the study. We included in the study only those children who had a lumbar puncture performed, using fixed 50% nitrous oxide–oxygen mixture as the only analgesic or in combination with other methods of analgesia. Physicians were asked to complete a questionnaire immediately after performing the lumbar puncture. The following factors were recorded in said questionnaire: demographic data; drug association; evaluation of pain; level of satisfaction of patients, parents, and sanitary staff; and the presence of adverse effects. Children were shown the Wong-Baker Faces Pain Scale (Fig. 1) or a 0- to 10-point numerical scale, according to their age, to score pain experienced after it. Procedural pain was also evaluated by the nurse, doctor and parents on a scale of 0 to 10. Parents were given the option to attend the procedure in every case. Staff satisfaction regarding EMONO efficacy was evaluated using a scale of 0 to 10. Doctors who carried out the procedure were also asked if they thought that EMONO inhalation had facilitated the procedure.

Usually, it was the patient who held the mask during the process. Heart and respiratory rates and oxygen saturation were monitored, and the level of sedation as well as other symptoms, such as pain, nausea, or vomiting, was noted throughout the procedure.

Children who attended the emergency department more than once during the study period were included separately for each visit in which a lumbar puncture was performed.

RESULTS

We collected data on 39 lumbar punctures performed using fixed 50% nitrous oxide–oxygen mixture during the study period. The median patient age was 8.1 years (range, 2–12 years). Sixty-one percent of the patients were male. Seven children (18%) received fixed 50% nitrous oxide–oxygen mixture as only analgesia, and 32 (82%) received both topical anesthetic agent EMLA cream (eutectic mixture of local anesthetics, lidocaine, and prilocaine) and fixed 50% nitrous oxide–oxygen mixture. Pain evaluations during the procedure for the whole sample are shown in Table 1. Table 2 shows expected

TABLE 1. Procedural Pain Intensity Assessed by Children, Nurses, Doctors, and Parents During EMONO Inhalation

<table>
<thead>
<tr>
<th>No. Patients Evaluated</th>
<th>Pain Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Children 4–6 y (Faces Pain Rating Scale 0–10)</td>
<td>7</td>
</tr>
<tr>
<td>Children &gt;6 y (0- to 10-point numerical scale)</td>
<td>25</td>
</tr>
<tr>
<td>Nurse (0- to 10-point numerical scale)</td>
<td>17</td>
</tr>
<tr>
<td>Doctor (0- to 10-point numerical scale)</td>
<td>31</td>
</tr>
<tr>
<td>Parent (0- to 10-point numerical scale)</td>
<td>18</td>
</tr>
</tbody>
</table>
TABLE 2. Expected and Experienced Pain Assessed by Children Before and After the Procedure

<table>
<thead>
<tr>
<th>Pain Assessment</th>
<th>No. of Patients</th>
<th>Median</th>
<th>Interquartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected pain</td>
<td>21</td>
<td>4</td>
<td>2–8</td>
</tr>
<tr>
<td>Experienced pain</td>
<td>32</td>
<td>2</td>
<td>0–3</td>
</tr>
</tbody>
</table>

Given that lumbar puncture is usually an emergency procedure, it is important to note that the preparation for a given case is quick, because the extra equipment that is required can be kept in the emergency department, and no fasting is required as there is no loss of reflexes as long as the concentration of the gas is kept below 50% and hypnotic sedatives are not simultaneously administered.

Although our study is too small to be a “safety study,” it adds to the many reports that have already shown the wide margin of safety in using inhaled nitrous oxide in the pediatric population. However, it should be underlined that although inhaled nitrous oxide use is safe, patients should always be clinically monitored by a dedicated staff member.

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REFERENCES


Concentrated Midazolam for Intranasal Administration

A Pilot Study

To the Editors:

Light procedural sedation and anxiolysis can be successfully achieved by using intranasal (IN) drugs. This strategy allows avoiding the need for intravenous access in frightened or uncooperative children. Minimizing drug volume while maximizing drug concentration can be crucial to have a successful IN delivery, whereas volumes in excess of 1 mL per nostril are not reliably absorbed as a result of mucosal surface saturation and runoff from the nasal cavity. 1

Midazolam is the most common benzodiazepine used for procedural sedation and analgesia. Previous pediatric IN midazolam studies have shown safety and efficacy of IN delivery of the drug for procedural conscious sedation.2–8 Intranasal midazolam (INM) is typically dosed at 0.3 to 0.5 mg/kg (with a maximum of 15 mg). Usual formulation of midazolam for IN administration is the same used for intravenous route (5 mg/mL), but this formulation will result in high volumes in children older than 4 years. Moreover,

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the IN delivery of midazolam can cause pain, because of a mucosal irritating effect (result of the low pH) and bitter taste in up to 66% of patients, making the experience unpleasant and producing discomfort in the child.9-11

To guarantee a high drug dosage in a low volume and maximize the drug effect, we have set up a procedure to obtain a concentrated (10 mg/mL) stable isotonic midazolam solution by means of a midazolam chloride powder buffered in an adequate solution without benzyl alcohol. This solution is stable over 45 days, and stability over the time is still in progress. The pH of the 10-mg/mL solution is 3.5 versus less than 3.0 of the intravenous-use one.

Our program is to perform a prospective clinical trial comparing the usual intravenous formulation and the concentrated solution to evaluate differences in efficacy, tolerability, and adverse effects. Before starting the clinical trial, we performed a pilot study with concentrated midazolam on 40 children who underwent procedural conscious sedation in the emergency department (ED) of our tertiary pediatric hospital. The risks, possible discomforts, and benefits were explained to the parents, and they were required to sign an informed consent form before the procedure. Patients were excluded if they were younger than 1 month or if they had received other sedative medication in the previous 12 hours or had disabling systemic or respiratory disease, a coincidental head injury requiring hospital admission, or known allergy to midazolam or to other anesthetics. Patients received a dosage between 0.3 and 0.8 mg/kg (maximum dose of 20 mg). All sedations performed in the ED adhered to the hospital sedation policy, which includes requirements for monitoring, dedicated personnel, and recovery. A mucosal atomizing device was used to administer midazolam intranasally. A visual analog scale consisting of a 100-mm line marked from 0 to 10 (0 = no pain, 10 = worst imaginable pain) was used by parents and patients older than 6 years to evaluate patient discomfort due to INM administration. Successful anxiolysis was measured using an anxiety score previously validated based on observation of the child’s behavior. An anxiety score of 1 or 2 was deemed as “effective sedation.” A telephone questionnaire was performed at 2 to 15 days after the procedure. Parents were asked about the child’s well-being and the incidence of adverse effects and amnesia. A subjective opinion on the success of the midazolam was then sought. They were also asked if they would like the same drug to be used if the child attended the ED again under similar circumstances. Safety was evaluated by the need of medical intervention for airway support, oxygen supplementation, and use of rescue medication.

The patient population was 63% male, with a mean age of 52 months and a range of 5 months to 12 years. The mean midazolam dose was 0.58 mg/kg (range, 0.3–0.8 mg/kg). Laceration repair was the procedure most commonly performed (65%); other procedures included difficult intravenous access, wound or burn medication, fracture reduction, and frenulotomy. Visual analog scale score during IN delivery resulted to less than 5 in 33 children (82.5%). According to judgment of parents (n = 32) who had experienced nasal washing with normal saline solution, the procedure was not considered more bothersome with no specific complaint. During the procedure, an effective sedation was reached in 35 patients (87.5%). The mean time from administration of midazolam to readiness for procedure was 12 minutes (range, 10–22 minutes). The mean time to discharge was 94 minutes (range, 60–235 minutes). There were no major adverse effects (desaturation, need for airway support or for rescue medication, paradoxical hyperagitation) documented in the ED or reported at follow-up, except in only 1 patient in whom duration of sedation was long enough (4 hours) to create some discomfort in the patient. Telephone follow-up questionnaires were completed in 35 children (87.5%). From the patients completed follow-up questionnaires, 30 (85.7%) of children had lost some memory of the event and had not expressed any negative feelings about it. Thirty-one parents (n = 31, 88.6%) said they would like the same medicine to be used again if similar circumstances arose.

Degree of sedation was sufficient to complete the procedure in the majority of patients, confirming results of previous studies. In nearly all patients, the advantage of amnesia was obtained as confirmed by parents in a telephone follow-up. No major adverse events were observed.

In this pilot study with concentrated INM, we have observed significant discomfort only in a minority (17.5%) of patients during IN delivery, and this is probably the result of reduced volume, of the lack of benzyl alcohol, and of a small increase in the pH of the solution. The reduced volume probably reduces the amount of the drug that runs off from the nasal cavity and the perception of a bitter taste in the pharynx.

Concentrated midazolam seems to be advantageous for IN delivery to reduce administration discomfort. Furthermore, it allows maximum dosage (20 mg) with a volume that will not result in excess of 1 mL per nostril and the possibility, at low dosages and for smaller children, of the simultaneous administration in the second nostril of other drugs (IN fentanyl or ketamine). These preliminary data must be definitely confirmed by final results of comparative studies on tolerability of concentrated solution and usual formulation of midazolam. Nevertheless, in our experience, concentrated midazolam for IN use was safe, efficacious, and well tolerated.


